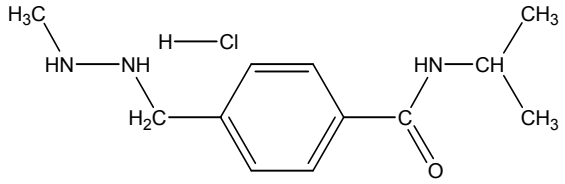
PROCARBAZINE HYDROCHLORIDE
CAS No. 366-70-1
First Listed in the *Second Annual Report on Carcinogens*



CARCINOGENICITY

Procarbazine hydrochloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (NCI 19, 1979; IARC V.26, 1981; IARC S.4, 1982; IARC S.7, 1987). The generic name procarbazine is used interchangeably with procarbazine hydrochloride in the literature, and since only procarbazine hydrochloride is produced, it was assumed to be procarbazine hydrochloride under study. When administered by repeated intraperitoneal injection, procarbazine hydrochloride induced olfactory neuroblastomas, adenocarcinomas of the mammary gland, and malignant lymphomas, lymphocytic type, in rats of both sexes, and olfactory neuroblastomas in mice of both sexes and uterine adenocarcinomas in female mice. When administered by gavage, the compound induced leukemia and benign tumors of the lung in mice of both sexes and adenocarcinomas or carcinomas of the mammary gland in female rats but not in male rats. When administered by repeated intravenous injections, the compound induced three renal sarcomas and two intra-abdominal spindle cell sarcomas in male rats. Male and female monkeys, including Rhesus, cynomolgus and African green monkeys, were given procarbazine hydrochloride by subcutaneous, intravenous, and oral routes. Rhesus monkeys developed acute myelogenous leukemia. Cynomolgus monkeys had leukemia or lymphoma, and multiple hemangiosarcomas. The rarity of neoplasms, and in particular leukemias (none in control monkeys in that colony), strongly suggests that procarbazine induced the tumors.

There is inadequate evidence for the carcinogenicity of procarbazine in humans . In various combinations with other chemotherapeutic agents given for Hodgkin's disease, procarbazine use has repeatedly been shown to lead to the appearance of acute nonlymphocytic leukemia. These combinations usually also include nitrogen mustard, an alkylating agent which is also a potent animal carcinogen, and these many observations do not permit conclusions about the independent effect of either drug.

PROPERTIES

Procarbazine hydrochloride is a white-to-pale yellow crystalline powder with a slight odor. It is sensitive to light. It is soluble but unstable in water and aqueous solutions. It degrades rapidly in alcoholic medias. When heated to decomposition, it emits very toxic fumes of nitrogen oxides (NO_x). It is available in the United States as a USP grade containing 98.5%-100.5% active ingredient.

USE

Procarbazine hydrochloride is used in human medicine as an antineoplastic and chemotherapeutic agent. It is used in combination with other antineoplastic agents to treat Hodgkin's disease and is also used to treat malignant melanoma, non-Hodgkin's lymphoma, and small-cell carcinomas of the lung (IARC V.26, 1981). FDA approved its use in 1969, indicating that the drug should be used as an adjunct to standard therapy.

PRODUCTION

The USITC identified two U.S. producers of procarbazine hydrochloride in 1988, but no production data were reported (USITC, 1989). The USITC reported that two U.S. companies produced an unknown quantity of procarbazine hydrochloride in 1986 (USITC, 1987). No other production, import, or export data were available. The 1979 TSCA Inventory reported no production data for procarbazine or its hydrochloride (TSCA, 1979).

EXPOSURE

The primary routes of potential human exposure to procarbazine hydrochloride are ingestion, inhalation, and dermal contact. For patients receiving the drug, the usual initial dose of procarbazine hydrochloride is 2-4 mg/kg body weight daily given orally in divided doses for 1 week, then 4-6 mg/kg body weight daily, until signs of bone marrow depression occur. After bone marrow recovery, treatment is resumed at a dose level of 1-2 mg/kg body weight per day (IARC V.26, 1981). Potential occupational exposure to procarbazine hydrochloride could occur during the manufacture, formulation, and packaging of the drug. The National Occupational Exposure Survey (1981-1983) indicated that 1,329 workers, including 289 women, potentially were exposed to procarbazine hydrochloride (NIOSH, 1984). This estimate was derived from observations of the actual use of the compound (89% of total observations) and of tradename products known to contain the compound (11%). Health professionals (e.g., physicians, nurses, pharmacists) are potentially exposed to the pharmaceuticals during preparation, administration, and cleanup. In 1980, the National Prescription Audit reported 1.5 million prescriptions dispensed for procarbazine hydrochloride. Some of the metabolites of procarbazine are both carcinostatic and carcinogenic.

REGULATIONS

Procarbazine hydrochloride is used primarily as a pharmaceutical and is produced in low quantities relative to other chemicals; therefore, it is of little regulatory concern to EPA. However, there may be a small pollution problem relative to hospital wastes. Procarbazine hydrochloride is approved as a prescription drug for treatment of Hodgkin's disease and for patients nonresponsive to other cancer treatments. It is subject to FDA prescription drug labeling requirements under the Food, Drug, and Cosmetic Act (FD&CA). OSHA regulates procarbazine hydrochloride under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-125.